REMARKS

Status of the Claims

Claims 29, 41, 42, 46, 85, 94, 95, 99, 101, 108, and 109 have been amended as noted below for the purpose of clarifying the characteristic features of the claimed compositions. No new matter is added by way of claim amendment.

Specifically, independent claims 29, 46, 85, 99, and 101 have been amended to recite an upper limit of about 200 mg/ml for the concentration of IGF-I or analogue thereof present within the claimed compositions. These claims now recite the concentration range that was presented as a limitation in dependent claims 41, 94, and 108. Accordingly, dependent claims 41, 94, and 108 have been amended to recite a concentration of IGF-I or analogue thereof in the range of about 15 mg/ml to about 200 mg/ml, and dependent claims 42, 95, and 109 have been amended to recite a concentration of IGF-I or analogue thereof in the range of about 20 mg/ml to about 200 mg/ml. Support for recitation of these concentration ranges resides in the specification, for example, at page 13, lines 1-5, and in the claims as originally filed. Independent claims 46 and 99 have also been amended to include the limitation that the solubilizing compound is present in the composition in an amount sufficient to make the IGF-I or analogue thereof soluble at a concentration of about 12 mg/ml to about 200 mg/ml when the composition is at a temperature of about 4°C. Support for this claim limitation resides throughout the specification and in the other independent claims as originally presented. The Examiner is respectfully requested to enter these claim amendments into the above-referenced application.

Claims 29-48 and 85-112 remain pending in the application. The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

Oath/Declaration

The Examiner states that a new oath or declaration in compliance with 37 CFR §1.67(a) identifying this application by application number and filing date is required. Applicants respectfully bring to the Examiner's attention that a substitute declaration in compliance with 37 CFR §1.67(a) was filed on September 17, 2002. For the Examiner's convenience, Applicants have enclosed a copy of the substitute declaration as filed on September 17, 2002.

The Provisional Obviousness-Type Double Patenting Rejection Should Be Withdrawn

Claims 29-40, 44-48, 85-93, 97-107, 111, and 112 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 5, 10-14, 16, 17, 18, and 20 of copending Application No. 09/187,661. This rejection is respectfully traversed.

The presently claimed invention is directed to compositions having a pH of about pH 5.5 or greater that comprise biologically active IGF-I or biologically active analogue thereof at a concentration of about 12 mg/ml to about 200 mg/ml when the composition is at a temperature of about 4°C and a solubilizing compound comprising a guanidinium group. The presence of the solubilizing compound makes the IGF-I or analogue thereof soluble at the recited concentration when the composition is at a temperature of about 4°C. Applicants respectfully submit that this composition is patentably distinct from the claimed compositions of copending Application No. 09/187,661.

In contrast, the claims of the 09/187,661 application are directed to low-salt containing aqueous compositions that comprise biologically active human IGF-I or biologically active variant thereof in a concentration of at least 250 mg/ml and which have a pH greater than about pH 5.0. The specification of the 09/187,661 application teaches that the IGF-I or variant thereof is present in these compositions in a highly concentrated form that has the consistency of a viscous syrup. See, for example, the Summary of the Invention, paragraph one of the Detailed Description, and the Abstract. Those compositions are prepared by precipitating IGF-I or variant thereof from solution. In one embodiment, the method of preparation comprises the addition of a solubility enhancer to a solution to allow for preparation of a solution comprising a high concentration of IGF-I or variant thereof, followed by removal of the solubility enhancer from this solution, for example, by dialysis or diafiltration. The specification teaches that suitable solubility enhancers are compounds that include a guanidinium group. Removal of the solubility enhancer from the high-concentration IGF-I solution results in precipitation of the IGF-I or variant thereof as the highly concentrated syrup form that is recited in the claims of the 09/187,661 application. Because the solubility enhancer has been removed from the solution in order to precipitate out the IGF-I protein or variant thereof, the compositions recited in the claims of the 09/187,661 application do not contain the solubilizing compound in the manner

recited in the presently claimed compositions, otherwise the IGF-I or variant thereof would be present in its soluble form at a concentration of about 12 mg/ml to about 200 mg/ml.

In support of Applicants' contention that the presently claimed compositions are patentably distinct from the compositions recited in the claims of copending Application No. 09/187,661, claims 41-43, 94-96, and 108-110 of the present invention were not subject to this rejection. These claims all include the limitation that the upper concentration of IGF-I or analogue thereof is about 200 mg/ml.

As the presently claimed compositions are patentably distinct from the compositions claimed in copending Application No. 09/187,661, Applicants respectfully submit that this obviousness-type double patenting rejection should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner advises Applicants of the obligation under 37 CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

Claims 29-44, 46-48, 85-97, and 99-111 are rejected under 35 U.S.C. §103 as being unpatentable over Florin-Robertsson *et al.* (WO 94/15584) taken with Ron *et al.* (U.S. Patent No. 5,597,897). This rejection is respectfully traversed.

The presently claimed invention is directed to IGF-I compositions in which IGF-I is highly soluble at a pH of 5.5 or greater and highly soluble when the composition is stored at 4°C. Physical parameters such as temperature and pH affect the solubility of IGF-I. For example, below about pH 5.0, IGF-I is soluble at concentrations of about 80-100 mg/ml while above pH 5.5 the solubility drops about ten-fold. Additionally, IGF-I is less soluble at lower temperatures. Thus, in order to provide IGF-I compositions capable of refrigerated storage, e.g., to retain stability, while still maintaining acceptable IGF-I solubility levels, compositions are now generally formulated at a non-physiological pH of less than 5.0. Unfortunately, administration of IGF-I compositions having a non-physiological pH causes pain and irritation at the site of injection. As provided on page 7, lines 19 – 33 of the specification, the presently claimed

invention solves this problem through the addition of a "solubilizing compound" that includes a guanidinium group to IGF-I compositions such that IGF-I is highly soluble at a pH of 5.5 or greater and when the composition is stored at 4°C. Applicants respectfully submit that the cited references alone or in combination do not teach or suggest the addition of a "solubilizing compound" that includes a guanidinium group to IGF-I compositions in accordance with the claims of the present invention.

To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Applicants respectfully submit that when establishing a *prima facie* case of obviousness, one must consider the teachings of the cited reference(s) as a whole, including portions that would lead away from the claimed invention. MPEP §2141.02. It is Applicants' contention that a *prima facie* case of obviousness has not been established in the present application as the motivation to modify either one of these references, or to combine the teachings of these references, to arrive at Applicants' claimed invention is lacking. Even if such motivation were to exist, these references do not provide to one of skill in the art a reasonable expectation of success.

Florin-Robertsson *et al.* serves as the primary reference cited by the Examiner. This reference teaches a stable solution containing IGF-I in 5-50 mM phosphate buffer having a pH of 5.5 to 6.5, which is isotonic. As noted by the Examiner, Florin-Robertsson *et al.* does not teach the use of a solubilizing compound comprising a guanidinium group in the formulation. However, the Examiner states that this addition would be obvious in light of Ron *et al.*, which teaches a pharmaceutically acceptable admixture of an osteogenic protein that may contain a solubilizing compound such as arginine or arginine methyl ester guanidine (at column 2, lines 38-42). However, Applicants respectfully submit that the addition of such a solubilizing compound to a composition comprising an osteogenic protein would not have led one of skill in the art to Applicants' discovery given the state of the art at the time of Applicants' invention. This point is exemplified by the prior art references cited in the Office Action, which, for reasons

outlined below, provide no motivation to travel down Applicants' path of inquiry that led to the presently claimed invention.

First, there is no suggestion or motivation to combine the teachings of these cited references. Florin-Robertsson *et al.* focuses specifically on solving problems associated with the stability of compositions comprising IGF-I. As stated in Florin-Robertsson *et al.*, "the problem to find a stable solution for IGF-I which does not hurt when injected has not until now been resolved. It has now been found that the pain is significantly reduced when a solution according to the invention is used" (at page 5, lines 12-16). In solving this problem, Florin-Robertsson *et al.* did not identify solubility as a potential solution but instead focused on the type and molarity of buffer, and the effect of certain pH ranges on such compositions (at page 5, lines 20-36 and page 6, lines 1-9). The only reference to solubility contained in Florin-Robertsson *et al.* is the statement that "the concentration of IGF-I is only dependent of ~~sic~~ its solubility in the used buffer and the desired therapeutically ~~sic~~ amount for the given dose" (at page 7, lines 24-25). Applicants respectfully contend that one of skill in the art would not interpret this statement as a recognition that modification of solubility could be used to solve the problem sought to be solved in Florin-Robertsson *et al.*, namely to find a stable solution for IGF-I that does not hurt when injected.

Motivation to combine the teachings of these two cited referenced is also lacking in Ron *et al.* Although Ron *et al.* discloses a pharmaceutically acceptable admixture that may contain a solubilizing compound, the motivation behind development and production of the composition centered on the specific characteristics of osteogenic proteins. As described in Ron *et al.*, osteogenic proteins are those proteins capable of inducing, or assisting in the induction of cartilage and/or bone formation (at column 1, lines 16-18). Insulin-like growth factor I is not identified by either Ron *et al.* or Florin-Robertsson *et al.* as being a member of this class of proteins. The objective of the invention in Ron *et al.* is "to sequester osteogenic protein in-situ for a time sufficient to allow the protein to induce cartilage and/or bone formation" (at column 1, lines 11-15). Thus, while Ron *et al.* may contain reference to the use of a solubilizing compound such as arginine or arginine methyl ester guanidine for osteogenic proteins, there is no motivation to apply this type of formulation to the stability problems identified by Florin-

Robertsson *et al.* surrounding IGF-I. Furthermore, given the unpredictability surrounding the formulation of proteins as further described below, one of skill in the art would not have recognized that formulations directed to osteogenic proteins could be used to solve problems associated with formulations directed to IGF-I.

Second, even if there was a motivation to combine the cited references, there is no reasonable expectation of success. Florin-Robertsson *et al.* describes some of the problems associated with pharmaceutical preparations that include proteins:

> Proteins are different with regard to physiological properties. When preparing a pharmaceutical preparation which should be physiologically acceptable, and stable for a long time, consideration can not only be taken to the physiological properties of the protein but also other aspects must be considered such as the industrial manufacture, easy handling for the patient and safety for the patient. The results of these aspects are not predictable when testing different formulations and each protein has often a unique solution regarding stability.

(at page 4, lines 16-23). Therefore, one of skill in the art would recognize that formulations for a given protein must take into account that protein's unique properties and cannot automatically be extrapolated to other, especially unrelated, proteins. Although Ron *et al.* discloses a pharmaceutically acceptable admixture that may contain a solubilizing compound, as described above the motivation behind development and production of the Ron *et al.* composition centers on the specific characteristics of osteogenic proteins. Given the recognition in Florin-Robertsson *et al.* of the unpredictability surrounding the formulation of different proteins, Ron *et al.* fails to provide evidence to suggest a reasonable expectation of success with respect to the application of its disclosed formulation to IGF-I.

Applicants respectfully submit that the Florin-Robertsson *et al.* and the Ron *et al.* references cannot serve as the basis for a *prima facie* case of obviousness. These references do not provide a motivation to one of skill in the art to combine the teachings disclosed therein to arrive at Applicants' claimed invention, nor would a reasonable expectation of success have been supported by the teachings of these cited references. For these reasons, Applicants

respectfully submit that a *prima facie* case of obviousness has not been established, and this rejection of the claims under 35 U.S.C. §103 should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the objection to the oath/declaration, the provisional obviousness-type double patenting rejection, and the rejection of the claims under 35 U.S.C. §103 are overcome. Accordingly, the present application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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